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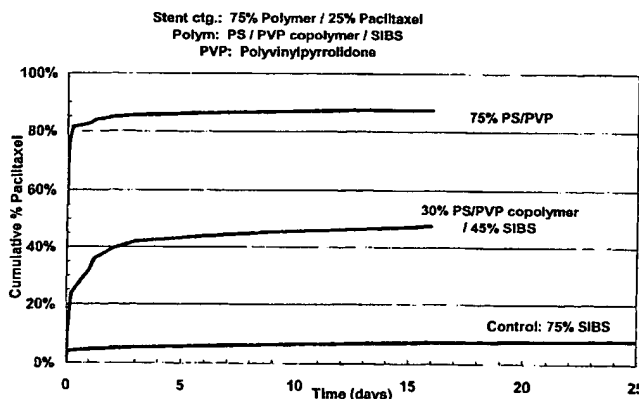
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(54) Title: **IMPLANTABLE OR INSERTABLE MEDICAL DEVICES FOR CONTROLLED DELIVERY OF A THERAPEUTIC AGENT**



(57) Abstract: The present invention is directed to novel implantable or insertable medical devices that provide release of a therapeutic agent. According to a first aspect of the present invention, a therapeutic-agent-releasing medical device is provided, which comprises: (a) an implantable or insertable medical device; (b) a release layer disposed over at least a portion of the implantable or insertable medical device, and (c) a therapeutic agent. The release layer regulates the rate of release of the therapeutic agent from the medical device upon implantation or insertion of the device into a patient. The release layer comprises (i) a first polymer comprising one or more polymer chains that form one or more polymer phase domains when the first polymer is in a pure solid-state form; and (ii) a second polymer comprising two or more polymer chains that form two or more phase domains when the second polymer is in a pure solid-state form. The first and second polymers are preferably selected such that at least one polymer chain in the second polymer is compatible with at least one polymer chain in the first polymer. The present invention is also directed to methods of forming the above implantable or insertable medical devices, methods of administering a therapeutic agent to a patient using such devices, and methods of modulating the release of therapeutic agents from implantable or insertable medical devices.

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IMPLANTABLE OR INSERTABLE MEDICAL DEVICES  
FOR CONTROLLED DELIVERY OF A THERAPEUTIC AGENT

FIELD OF THE INVENTION

[0001] The present invention relates to implantable or insertable medical devices for controlled delivery of one or more therapeutic agents.

BACKGROUND OF THE INVENTION

[0002] Numerous medical devices have been developed for the delivery of therapeutic agents to the body.

[0003] In accordance with some delivery strategies, a therapeutic agent is provided (a) within a polymeric carrier layer and/or (b) beneath a polymeric barrier layer that is associated with an implantable or insertable medical device. Once the medical device is placed at the desired location within a patient, the therapeutic agent is released from the medical device at a rate that is dependent upon the nature of the polymeric carrier and/or barrier layer.

[0004] The desired release profile for the therapeutic agent is dependent upon the particular treatment at hand, including the specific condition being treated, the specific therapeutic agent selected, the specific site of administration, and so forth. As a result, there is a continuing need for polymeric layers, including polymeric barrier layers and carrier layers, which are able to provide a broad range of therapeutic agent release rates.

SUMMARY OF THE INVENTION

[0005] According to a first aspect of the present invention, a therapeutic-agent-releasing medical device is provided, which comprises: (a) an implantable or insertable medical device; (b) a release layer disposed over at least a portion of the implantable or insertable medical device, and (c) a therapeutic agent. The release layer regulates the rate of release of the therapeutic agent from the medical device upon implantation or insertion of the device into a patient. The release layer comprises (i) a first polymer comprising one or more polymer chains that form one or more polymer phase domains when the first

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polymer is in a pure solid-state form; and (ii) a second polymer comprising two or more polymer chains that form two or more phase domains when the second polymer is in a pure solid-state form.

[0006] In preferred embodiments, the first and second polymers are selected such that at least one polymer chain in the second polymer is compatible with at least one polymer chain in the first polymer. Two polymer chains are said to be compatible with one another when the phases that correspond to these chains exhibit at least some degree of interfacial mixing, up to and including complete miscibility between the phases.

[0007] In some embodiments, the release layer is a carrier layer that comprises the therapeutic agent(s). In other embodiments, the release layer is a barrier layer disposed over a therapeutic-agent-containing region, which comprises the therapeutic agent.

[0008] Preferred medical devices include catheters, guide wires, balloons, filters, stents, stent grafts, vascular grafts, vascular patches, shunts, and intraluminal paving systems. The device can be adapted, for example, for implantation or insertion into the coronary vasculature, peripheral vascular system, esophagus, trachea, colon, biliary tract, urinary tract, prostate or brain.

[0009] Beneficial therapeutic agents for the practice of the present invention include anti-thrombotic agents, anti-proliferative agents, anti-inflammatory agents, anti-migratory agents, agents affecting extracellular matrix production and organization, antineoplastic agents, anti-mitotic agents, anesthetic agents, anti-coagulants, vascular cell growth promoters, vascular cell growth inhibitors, cholesterol-lowering agents, vasodilating agents, and agents that interfere with endogenous vasoactive mechanisms.

[0010] According to another aspect of the present invention, a method of making a therapeutic-agent-releasing medical device is provided. The method comprises: (a) providing a solution comprising: a solvent, a first polymer like that discussed above, and a second polymer like that discussed above; (b) applying the solution to a surface of an implantable or insertable medical device; and (c) removing the solvents from the solution to form a release layer. Solvent spraying is a preferred technique for applying the above solution.

[0011] In some embodiments (for example, where a carrier layer is being formed),

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the solution further comprises the therapeutic agent. In other embodiments (for example, where a barrier layer is being formed), the solution is applied over a therapeutic-agent-containing region that comprises the therapeutic agent.

[0012] According to another aspect of the present invention, a method of modulating the release rate of a therapeutic agent from a medical device is provided. The medical device comprises (a) an implantable or insertable medical device; (b) a release layer disposed over at least a portion of the implantable or insertable medical device; (c) a therapeutic agent. The release layer regulates the rate of release of the therapeutic agent from the medical device upon implantation or insertion of the device into a patient. The release layer also comprises a first polymer, which further comprises one or more polymer chains that form one or more polymer phase domains when the first polymer is in a pure solid-state form. The rate of release of the therapeutic agent from the medical device is modulated by adding to the release layer a second polymer, which comprises two or more polymer chains that form two or more phase domains when the second polymer is in a pure solid-state form.

[0013] In preferred embodiments, the second polymer is selected such that at least one polymer chain in the second polymer is compatible with at least one polymer chain in the first polymer.

[0014] One advantage of the present invention is that implantable or insertable medical devices are provided, which are able to provide therapeutic agent release over a wide variety of time frames.

[0015] Another advantage of the present invention is that effective strategies are provided for controlling, or "tuning," the release profile of a therapeutic agent from an implantable or insertable medical device.

[0016] These and other embodiments and advantages of the present invention will become immediately apparent to those of ordinary skill in the art upon review of the Detailed Description and Claims to follow.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Fig. 1 illustrates cumulative release of paclitaxel as a function of time for carrier layers containing (a) polystyrene-polyisobutylene-polystyrene triblock copolymer, (b) polystyrene-polyvinylpyrrolidone diblock copolymer, and (c) a blend of polystyrene-

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polyisobutylene-polystyrene triblock copolymer with polystyrene-polyvinylpyrrolidone diblock copolymer, in accordance with an embodiment of the present invention.

[0018] Fig. 2 illustrates cumulative release of paclitaxel as a function of time for carrier layers containing (a) a blend of polystyrene-polyisobutylene-polystyrene triblock copolymer and polystyrene-polyacrylic acid-polystyrene triblock copolymer, and (b) a blend of polystyrene-polyisobutylene-polystyrene block copolymer and polystyrene-polyacrylic acid diblock copolymer.

[0019] Fig. 3 illustrates cumulative release of paclitaxel as a function of time for carrier layers containing (a) a blend of polystyrene-polyisobutylene-polystyrene triblock copolymer and polystyrene-polyacrylamide diblock copolymer, and (b) a blend of polystyrene-polyisobutylene-polystyrene triblock copolymer and polystyrene-polyacrylate sodium salt diblock copolymer.

[0020] Fig. 4 illustrates cumulative release of paclitaxel as a function of time for carrier layers containing (a) a blend of polystyrene-polyisobutylene-polystyrene triblock copolymer and polystyrene-polyethylene oxide-polystyrene triblock copolymer, (b) a blend of polystyrene-polyisobutylene-polystyrene triblock copolymer and polyethylene oxide-polystyrene-polyethylene oxide triblock copolymer, and (c) blends of polystyrene-polyisobutylene-polystyrene triblock copolymer with two polystyrene-polyethylene oxide diblock copolymers.

#### DETAILED DESCRIPTION OF THE INVENTION

[0021] The present invention relates to implantable or insertable medical device which provide for the release of one or more therapeutic agents, methods for making such devices, and methods for modulating the rate at which therapeutic agent is released from such devices.

[0022] By "release layer" is meant a layer that regulates the rate of release of at least one therapeutic agent. Two preferred release layers for use in accordance with the present invention are carrier layers and barrier layers.

[0023] By "carrier layer" is meant a layer which contains at least one therapeutic agent and from which the therapeutic agent is released.

[0024] By "barrier layer" is meant a layer which is disposed between a source of

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therapeutic agent and a site of intended release and which controls the rate at which the therapeutic agent is released.

[0025] According to one aspect of the present invention, a therapeutic-agent-releasing medical device is provided, which comprises: (a) an implantable or insertable medical device; (b) a release layer disposed over at least a portion of the implantable or insertable medical device; and (c) a therapeutic agent. Upon implantation or insertion of the device into a patient, the release layer regulates the rate of release of the therapeutic agent from the device. Moreover, the release layer comprises the following: (i) a first polymer, which comprises one or more polymer chains that form one or more polymer phase domains when the first polymer is in a pure solid-state form; and (ii) a second polymer, which comprises two or more polymer chains that form two or more phase domains when the second polymer is in a pure solid-state form. At least one polymer chain in the second polymer is preferably compatible with at least one polymer chain in the first polymer.

[0026] According to another aspect of the present invention, a method of modulating the release rate of a therapeutic agent from a medical device is provided. The medical device comprises (a) an implantable or insertable medical device; (b) a release layer disposed over at least a portion of the implantable or insertable medical device; (c) a therapeutic agent. The release layer regulates the rate of release of the therapeutic agent from the medical device upon implantation or insertion of the device into a patient. The release layer also comprises a first polymer, which further comprises one or more polymer chains that form one or more polymer phase domains when the first polymer is in a pure solid-state form. The rate of release of the therapeutic agent from the medical device is modulated by adding to the release layer a second polymer, which comprises two or more polymer chains that form two or more phase domains when the second polymer is in a pure solid-state form. The second polymer is preferably selected such that at least one polymer chain in the second polymer is compatible with at least one polymer chain in the first polymer.

[0027] The first and second polymers described above can be formed from a wide variety of polymer chains, including: polycarboxylic acid chains, such as polyacrylic acid, acetal polymer chains, acrylate and methacrylate polymer chains, cellulosic chains including cellulose acetates, cellulose nitrates, cellulose propionates, cellulose butyrates,

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cellophanes, rayons, rayon triacetates, and cellulose ethers such as carboxymethyl celluloses and hydroxyalkyl celluloses, polyoxymethylenes, polyimides such as polyether block imides, polyamidimides, polyesterimides, and polyetherimides, polysulfone chains including polyarylsulfones and polyethersulfones, polyamide chains including nylon 6,6, polycaprolactams and polyacrylamides, polycarbonate chains, polyacrylonitrile chains, polyvinylpyrrolidone chains, polyvinyl chains including polyvinyl alcohols, polyvinyl halides such as polyvinyl chlorides, polyvinylacetate, polyvinylidene chlorides, polyvinyl ethers such as polyvinyl methyl ethers, polystyrenes, polyvinyl ketones, polyvinylcarbazoles, and polyvinyl esters such as polyvinyl acetates, polybenzimidazoles, polyalkyl oxide chains including polyethylene oxides (PEO); glycosaminoglycans; polyesters including polyethylene terephthalates and aliphatic polyesters such as polymer chains of lactide (which includes lactic acid as well as d-,l- and meso lactide), epsilon-caprolactone, glycolide (including glycolic acid), hydroxybutyrate, hydroxyvalerate, para-dioxanone, trimethylene carbonate (and its alkyl derivatives), 1,4-dioxepan-2-one, 1,5-dioxepan-2-one, and 6,6-dimethyl-1,4-dioxan-2-one, polyethers including polyarylethers such as polyphenylene ethers, polyether ketones, polyether ether ketones, polyphenylene sulfides, polyisocyanates, polyolefins including polyalkylenes such as polypropylenes, polyethylenes, polybutylenes (such as polybut-1-ene and polyisobutylene), poly-4-methyl-pen-1-enes, and polybutadienes, fluorinated polymers chains, including polytetrafluoroethylenes, polyhexafluoropropenes, and polyvinylidene fluorides, silicone polymer chains, polyurethane chains, p-xylylene polymer chains, polyiminocarbonates, polyphosphazines, polyalkylene oxalates, polyoxaamides and polyoxaesters (including those containing amines and/or amido groups), polyorthoesters, and biopolymer chains, such as polypeptides and polysaccharides. Chains containing two or more monomers from the above, which form a single phase domain when in a pure solid-state form (e.g., chains of random or alternating mixtures of two or more monomers) can also be used to form the first and second polymers.

[0028] Chains can also be made up from one or more of the following list (which is not exclusive to the above list) of monomers: (a) alkylene monomers, such as ethylene, propylene, butadiene, butylenes (e.g., butylene, isobutylene), and isoprene; (b) halogenated alkylene monomers (e.g., tetrafluoroethylene and chloroethylene); (c) vinyl monomers and derivatives, such as, methyl vinyl ether, vinyl acetate, vinyl ethylene

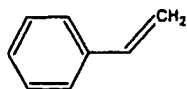
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(butadiene), vinyl chloride, vinyl pyrrolidone, vinyl cyanide (acrylonitrile), vinyl alcohol, and vinyl aromatics (e.g., styrene and styrene derivatives such as alpha-methyl styrene, ring-alkylated styrenes or ring-halogenated styrenes or other substituted styrenes where one or more substituents are present on the aromatic ring); (d) acrylic acid monomers and derivatives, such as methyl acrylate, methyl methacrylate, acrylic acid, methacrylic acid, hydroxyethyl acrylate, hydroxyethyl methacrylate, glyceryl acrylate, glyceryl methacrylate, acrylamide, methacrylamide and ethacrylamide and (e) maleic anhydride monomers and derivatives, including maleic anhydride, maleic anhydride in a free acid form, maleic anhydride in a salt form, and maleic anhydride in a partial ester form.

[0029] In some embodiments of the present invention, the first polymer will be a homopolymer, a random copolymer or an alternating copolymer, in which case a single phase domain will typically be formed when the first polymer is in a pure solid-state form.

[0030] In other embodiments, the first polymer will be a block copolymer or a graft copolymer, in which case multiple phase domains are typically formed.

[0031] Some specific exemplary first polymers for use in the present invention are block or graft copolymers comprising at least two polymer chains A and B. The A polymer chains are preferably soft elastomeric components which are based upon one or more polyolefins or other polymer with a glass transition temperature at or below room temperature, such as polymers of ethylene, propylene, butylene, isobutylene, and/or polybutadiene, or a silicone rubber block, an acrylate rubber block, and so forth. The B polymer chains are preferably hard thermoplastic chains with glass transition temperatures significantly higher than the elastomeric A block that, when combined with the soft A chains, are capable of, *inter alia*, altering or adjusting the hardness of the resulting copolymer to achieve a desired combination of qualities. Preferred B polymer chains are polymers of vinyl aromatics, such as chains made from monomers of styrene



and/or styrene derivatives (e.g.,  $\alpha$ -methylstyrene, ring-alkylated styrenes or ring-halogenated styrenes or other substituted styrenes where one or more substituents are present on the aromatic ring), collectively referred to herein as "styrenic blocks" or "styrenic chains".

[0032] Examples include diblock copolymers, triblock copolymers, star copolymers,



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and branched block copolymers, for example, dendritic block copolymers (e.g., arborescent block copolymers) wherein at least one of the A and B chains is branched, and preferably wherein the A chains are branched and capped by the B chains.

[0033] In some particularly preferred embodiments of the present invention the first polymer is selected from (a) polystyrene-polyisobutylene-polystyrene triblock copolymers (these polymers typically form two phase domains when the first polymer is in a pure solid-state form--a phase domain corresponding to the polystyrene polymer chains and a phase domain corresponding to the polyisobutylene polymer chain), which, along with other polymers appropriate for the practice of the present invention, are described, for example, in U.S. Patent No. 5,741,331, U.S. Patent No. 4,946,899 and U.S. Serial No. 09/734,639, each of which is hereby incorporated by reference in its entirety; (b) arborescent polyisobutylene-polystyrene block copolymers such as those described in Kwon et al., "Arborescent Polyisobutylene-Polystyrene Block Copolymers-a New Class of Thermoplastic Elastomers," *Polymer Preprints*, 2002, 43(1), 266, the entire disclosure of which is incorporated by reference, and (c) a copolymer containing one or more blocks of polystyrene and one or more random polymer blocks of ethylene and butylene, for example, a polystyrene-polyethylene/butylene-polystyrene (SEBS) block copolymer, available as Kraton™ G series polymers available from Kraton Polymers.

[0034] The second polymer is preferably a block copolymer or a graft copolymer containing two or more polymer chains, which give rise to two or more phase domains when the first polymer is in a pure solid-state form. As previously noted, the second polymer is preferably selected such that least one polymer chain in the second polymer is compatible with at least one polymer chain in the first polymer. More preferably, the same monomer or monomers are used to form the compatible polymer chains in both the first and second polymers.

[0035] For example, continuing with the specific example above in which the first polymer is a polystyrene-polyisobutylene-polystyrene triblock copolymer, it is preferred that the second polymer contain (a) one or more chains of polyisobutylene and/or (b) one or more chains of polystyrene.

[0036] Examples of second polymers containing one or more chains of polyisobutylene include block copolymers and graft copolymers comprising (i) one or more polyisobutylene chains and (ii) one or more chains selected from polyethylene

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oxide; polyvinylpyrrolidone; polyacrylamide; polydimethylacrylamide; polyacrylic acid and salts thereof; polymethacrylic acid and salts thereof; poly(maleic anhydride) and partial esters, free acids and acid salts thereof; polyvinyl alcohol and fully and partially hydrolyzed derivatives thereof; and poly(vinyl pyridine).

[0037] Examples of second polymers containing one or more chains of polystyrene include block copolymers and graft copolymers comprising (i) one or more chains of polystyrene and (ii) one or more chains selected from polyethylene oxide; polyvinylpyrrolidone; polyacrylamide; polydimethylacrylamide; polyacrylic acid and salts thereof; polymethacrylic acid and salts thereof; poly(maleic anhydride) and partial esters, free acids and acid salts thereof; polyvinyl alcohol and fully and partially hydrolyzed derivatives thereof; and poly(vinyl pyridine).

[0038] The table below lists several specific copolymers for use in connection with the present invention:

Polymer	Mol. Wt.	Source
PIB-PEO diblock copolymer	5kDa - 15kDa	PSI
PS-PEO diblock copolymer	11kDa - 41.9kDa	PSI
PS-PEO diblock copolymer	58.6kDa - 71kDa	PSI
PS-PEO-PS triblock copolymer	9.5kDa - 48kDa - 9.5kDa	PSI
PEO-PS-PEO triblock copolymer	6.3kDa - 1.7kDa - 6.3kDa	PSI
PVP-PS diblock copolymer	100kDa (overall)	ISP
PS-P(NaAc) diblock copolymer	3.5kDa - 34.5kDa	PSI
PS-PA diblock copolymer	16.5kDa - 4.4kDa	PSI
PS-PAA-PS triblock copolymer	2.5kDa - 22.8kDa - 2.5kDa	PSI
PS-PAA diblock copolymer	4.5kDa - 22.8kDa	PSI
PS-P(NaMeAc) diblock copolymer		PSI
PS-PDM diblock copolymer		PSI
PS grafted PEO copolymer		PSI
PS grafted PA copolymer		PSI
PS-PEO diblock copolymer	3.8kDa - 6.5kDa	PSI
PS-PEO diblock copolymer	4.6kDa - 12.2kDa	PSI

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Abbreviations: PIB = polyisobutylene  
PS = polystyrene  
PEO = polyethylene oxide  
PVP = polyvinylpyrrolidone  
P(NaAc) = polyacrylate sodium salt  
P(NaMeAc) = polymethacrylate sodium salt  
PDM = polydimethylacrylamide  
PA = polyacrylamide  
PAA = polyacrylic acid  
PSI = Polymer Source Inc., Dorval, Quebec, Canada  
ISP = International Specialty Products, Wayne, NJ, USA

[0039] In accordance with certain embodiments of the invention, the hydrophobic/hydrophilic balance of a release layer comprising a first polymer like that described above can be modulated (or “tuned”) by adding a second polymer like that described above. This change in the hydrophobic/hydrophilic balance of the release layer is accompanied by a change in the rate of release of therapeutic agent.

[0040] As an example, a release layer, which comprises a first polymer consisting one or more hydrophilic polymer chains, can be rendered more hydrophobic by adding a second polymer, which comprises (a) one or more hydrophilic polymer chains that are compatible with the hydrophilic polymer chains within the first polymer and (b) one or more hydrophobic polymer chains.

[0041] As used herein, a “hydrophilic polymer chain” is one that is more compatible with water and/or more polar in nature compared to other polymer chains while a “hydrophobic polymer chain” is one that is less compatible with water and/or less polar in nature compared to other polymer chains.

[0042] Conversely, as another specific example, a release layer, which comprises a first polymer that consists of one or more hydrophobic polymer chains, can be rendered more hydrophilic by adding a second polymer that comprises (a) one or more hydrophobic polymer chains that are compatible with the hydrophobic polymer chains within the first polymer and (b) one or more hydrophilic polymer chains.

[0043] For instance, release layers comprising a first polymer that contains polyisobutylene and polystyrene chains, both of which are hydrophobic (see, e.g., the polystyrene-polyisobutylene-polystyrene triblock copolymer of the Examples), can be rendered more hydrophilic by adding block copolymers which comprise (a) one or more

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polystyrene chains (which are hydrophobic and compatible with the polystyrene chains within the triblock copolymer) and (b) one or more hydrophilic polymer chains, such as the following: (i) polyvinylpyrrolidone (see, e.g., the polystyrene-polyvinylpyrrolidone diblock copolymer of Example 1), (ii) polyacrylic acid and its salts (see, e.g., the polystyrene-polyacrylic acid diblock copolymer of Example 2, the polystyrene-polyacrylic acid-polystyrene triblock copolymer of Example 2, and the polystyrene-sodium polyacrylate diblock copolymer of Example 3), (iii) polyacrylamide (see, e.g., the polystyrene-polyacrylamide diblock copolymer of Example 3), and (iv) polyethylene oxide (see, e.g., the polystyrene-polyethylene oxide-polystyrene triblock copolymer of Example 4, the polyethylene oxide-polystyrene-polyethylene oxide triblock copolymer of Example 4, and the polystyrene-polyethylene oxide diblock copolymer of Example 4).

[0044] These specific embodiments are advantageous for several reasons including the following: (1) Because the first polymer contains only hydrophobic polymer chains, and because the second polymer contains at least one hydrophilic polymer chain, the release layer is rendered more hydrophilic upon the addition of the second polymer. This typically results in a modulation of the drug release rate from the release layer. (2) Also, hydrophilic polymer chains, such as polyethylene oxide chains, are commonly prone to dissolution from release layers upon implantation/insertion, due to their compatibility with the surrounding aqueous environment. However, by attaching the hydrophilic polymer chain to a hydrophobic polymer chain (e.g., by attaching polyethylene oxide to polystyrene), the hydrophilic polymer chain is "anchored" by the hydrophobic polymer chain, rendering the hydrophilic polymer chain less prone to dissolution into a surrounding aqueous environment.

[0045] Hence, by following the above and analogous principles, the hydrophilic/hydrophobic balance of a release layer containing a first polymer like that described above can be altered by adding a second polymer like that described above. Whether or not the release layer will be rendered more hydrophilic or more hydrophobic upon the addition of the second polymer will depend upon on the composition and length of the polymer chains that are present within the first and second polymers.

[0046] The release rate can also be modulated by varying the composition and/or length of the polymer chains within the second polymer. As a specific example, a release layer comprising a polystyrene-polyisobutylene-polystyrene triblock copolymer as a first

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polymer and a polystyrene-polyethylene oxide block copolymer as a second polymer can be rendered more hydrophilic by either (a) substituting a more hydrophilic polymer chain for the polyethylene oxide chain within the polystyrene-polyethylene oxide block copolymer, or (b) increasing the length of the polyethylene oxide chain within the polystyrene-polyethylene oxide block copolymer.

[0047] In some of the above embodiments, the hydrophilic/hydrophobic balance of the release layer is changed in accordance with the present invention to modulate the release rate. However, other characteristics of the release layer besides hydrophilicity (or hydrophobicity, if viewed from the opposite perspective), for example, the overall polarity or ionic character of the release layer, may be modified by changing the nature of the second polymer (for example, by changing the length and/or composition of the polymer chains within the second polymer).

[0048] Preferred implantable or insertable medical devices for use in connection with the release layers of the present invention include catheters (for example, renal or vascular catheters such as balloon catheters), guide wires, balloons, filters (*e.g.*, vena cava filters), stents (including coronary vascular stents, cerebral, urethral, ureteral, biliary, tracheal, gastrointestinal and esophageal stents), stent grafts, cerebral aneurysm filler coils (including GDC--Guglielmi detachable coils--and metal coils), vascular grafts, myocardial plugs, patches, pacemakers and pacemaker leads, heart valves, biopsy devices, or any coated substrate (which can comprise, for example, glass, metal, polymer, ceramic and combinations thereof) that is implanted or inserted into the body, either for procedural use or as an implant, and from which therapeutic agent is released.

[0049] The medical devices contemplated for use in connection with the present invention include drug delivery medical devices that are used for either systemic treatment or for the localized treatment of any mammalian tissue or organ. Non-limiting examples are tumors; organs including but not limited to the heart, coronary and peripheral vascular system (referred to overall as "the vasculature"), lungs, trachea, esophagus, brain, liver, kidney, bladder, urethra and ureters, eye, intestines, stomach, pancreas, ovary, and prostate; skeletal muscle; smooth muscle; breast; cartilage; and bone.

[0050] One particularly preferred medical device for use in connection with the

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present invention is a vascular stent, which delivers therapeutic agent into the vasculature, for example, in the treatment of restenosis. As used herein, "treatment" refers to the prevention of a disease or condition, the reduction or elimination of symptoms associated with a disease or condition, or the substantial or complete elimination a disease or condition. Preferred subjects are mammalian subjects and more preferably human subjects.

[0051] "Therapeutic agents", "pharmaceutically active agents", "pharmaceutically active materials", "drugs" and other related terms may be used interchangeably herein and include genetic therapeutic agents, non-genetic therapeutic agents and cells. Therapeutic agents may be used singly or in combination.

[0052] Exemplary non-genetic therapeutic agents for use in connection with the present invention include: (a) anti-thrombotic agents such as heparin, heparin derivatives, urokinase, and PPACK (dextrophenylalanine proline arginine chloromethylketone); (b) anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine and mesalamine; (c) antineoplastic/antiproliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, angiopeptin, monoclonal antibodies capable of blocking smooth muscle cell proliferation, and thymidine kinase inhibitors; (d) anesthetic agents such as lidocaine, bupivacaine and ropivacaine; (e) anti-coagulants such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, hirudin, antithrombin compounds, platelet receptor antagonists, anti-thrombin antibodies, anti-platelet receptor antibodies, aspirin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet peptides; (f) vascular cell growth promoters such as growth factors, transcriptional activators, and translational promoters; (g) vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; (h) protein kinase and tyrosine kinase inhibitors (e.g., tyrphostins, genistein, quinoxalines); (i) prostacyclin analogs; (j) cholesterol-lowering agents; (k) angiopoietins; (l) antimicrobial agents such as triclosan, cephalosporins, aminoglycosides and nitrofurantoin; (m) cytotoxic agents, cytostatic

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agents and cell proliferation effectors; (n) vasodilating agents; and (o) agents that interfere with endogenous vasoactive mechanisms.

[0053] Exemplary genetic therapeutic agents for use in connection with the present invention include anti-sense DNA and RNA as well as DNA coding for: (a) anti-sense RNA, (b) tRNA or rRNA to replace defective or deficient endogenous molecules, (c) angiogenic factors including growth factors such as acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor  $\alpha$  and  $\beta$ , platelet-derived endothelial growth factor, platelet-derived growth factor, tumor necrosis factor  $\alpha$ , hepatocyte growth factor and insulin-like growth factor, (d) cell cycle inhibitors including CD inhibitors, and (e) thymidine kinase ("TK") and other agents useful for interfering with cell proliferation. Also of interest is DNA encoding for the family of bone morphogenic proteins ("BMP's"), including BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are any of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 and BMP-7. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Alternatively, or in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedgehog" proteins, or the DNA's encoding them.

[0054] Vectors for delivery of genetic therapeutic agents include (a) plasmids, (b) viral vectors such as adenovirus, adenoassociated virus and lentivirus, and (c) non-viral vectors such as lipids, liposomes and cationic lipids.

[0055] Cells for use in connection with the present invention include cells of human origin (autologous or allogeneic), including stem cells, or from an animal source (xenogeneic), which can be genetically engineered, if desired, to deliver proteins of interest.

[0056] Numerous therapeutic agents, not necessarily exclusive of those listed above, have been identified as candidates for vascular treatment regimens, for example, as agents targeting restenosis. Such agents are useful for the practice of the present invention and include one or more of the following: (a) Ca-channel blockers including benzothiazapines such as diltiazem and clentiazem, dihydropyridines such as nifedipine, amlodipine and nicardapine, and phenylalkylamines such as verapamil, (b) serotonin

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pathway modulators including: 5-HT antagonists such as ketanserin and naftidrofuryl, as well as 5-HT uptake inhibitors such as fluoxetine, (c) cyclic nucleotide pathway agents including phosphodiesterase inhibitors such as cilostazole and dipyridamole, adenylate/Guanylate cyclase stimulants such as forskolin, as well as adenosine analogs, (d) catecholamine modulators including  $\alpha$ -antagonists such as prazosin and bunazosine,  $\beta$ -antagonists such as propranolol and  $\alpha/\beta$ -antagonists such as labetalol and carvedilol, (e) endothelin receptor antagonists, (f) nitric oxide donors/releasing molecules including organic nitrates/nitrites such as nitroglycerin, isosorbide dinitrate and amyl nitrite, inorganic nitroso compounds such as sodium nitroprusside, sydnonimines such as molsidomine and linsidomine, nonoates such as diazenium diolates and NO adducts of alkanediamines, S-nitroso compounds including low molecular weight compounds (e.g., S-nitroso derivatives of captopril, glutathione and N-acetyl penicillamine) and high molecular weight compounds (e.g., S-nitroso derivatives of proteins, peptides, oligosaccharides, polysaccharides, synthetic polymers/oligomers and natural polymers/oligomers), as well as C-nitroso-compounds, O-nitroso-compounds, N-nitroso-compounds and L-arginine, (g) ACE inhibitors such as cilazapril, fosinopril and enalapril, (h) ATII-receptor antagonists such as saralasin and losartin, (i) platelet adhesion inhibitors such as albumin and polyethylene oxide, (j) platelet aggregation inhibitors including aspirin and thienopyridine (ticlopidine, clopidogrel) and GP IIb/IIIa inhibitors such as abciximab, eptifibatide and tirofiban, (k) coagulation pathway modulators including heparinoids such as heparin, low molecular weight heparin, dextran sulfate and  $\beta$ -cyclodextrin tetradecasulfate, thrombin inhibitors such as hirudin, hirulog, PPACK(D-phe-L-propyl-L-arg-chloromethylketone) and argatroban, FXa inhibitors such as antistatin and TAP (tick anticoagulant peptide), Vitamin K inhibitors such as warfarin, as well as activated protein C, (l) cyclooxygenase pathway inhibitors such as aspirin, ibuprofen, flurbiprofen, indomethacin and sulfinpyrazone, (m) natural and synthetic corticosteroids such as dexamethasone, prednisolone, methprednisolone and hydrocortisone, (n) lipoxigenase pathway inhibitors such as nordihydroguaiaretic acid and caffeic acid, (o) leukotriene receptor antagonists, (p) antagonists of E- and P-selectins, (q) inhibitors of VCAM-1 and ICAM-1 interactions, (r) prostaglandins and analogs thereof including prostaglandins such as PGE1 and PGI2 and prostacyclin analogs such as ciprostone, epoprostenol, carbacyclin, iloprost and beraprost, (s) macrophage activation



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preventers including bisphosphonates, (t) HMG-CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin and cerivastatin, (u) fish oils and omega-3-fatty acids, (v) free-radical scavengers/antioxidants such as probucol, vitamins C and E, ebbselen, trans-retinoic acid and SOD mimics, (w) agents affecting various growth factors including FGF pathway agents such as bFGF antibodies and chimeric fusion proteins, PDGF receptor antagonists such as trapidil, IGF pathway agents including somatostatin analogs such as angiopeptin and ocreotide, TGF- $\beta$  pathway agents such as polyanionic agents (heparin, fucoidin), decorin, and TGF- $\beta$  antibodies, EGF pathway agents such as EGF antibodies, receptor antagonists and chimeric fusion proteins, TNF- $\alpha$  pathway agents such as thalidomide and analogs thereof, Thromboxane A2 (TXA2) pathway modulators such as sulotroban, vapiprost, dazoxiben and ridogrel, as well as protein tyrosine kinase inhibitors such as tyrphostin, genistein and quinoxaline derivatives, (x) MMP pathway inhibitors such as marimastat, ilomastat and metastat, (y) cell motility inhibitors such as cytochalasin B, (z) antiproliferative/antineoplastic agents including antimetabolites such as purine analogs(6-mercaptopurine), pyrimidine analogs (e.g., cytarabine and 5-fluorouracil) and methotrexate, nitrogen mustards, alkyl sulfonates, ethylenimines, antibiotics (e.g., daunorubicin, doxorubicin), nitrosoureas, cisplatin, agents affecting microtubule dynamics (e.g., vinblastine, vincristine, colchicine, paclitaxel and epothilone), caspase activators, proteasome inhibitors, angiogenesis inhibitors (e.g., endostatin, angiostatin and squalamine), rapamycin, cerivastatin, flavopiridol and suramin, (aa) matrix deposition/organization pathway inhibitors such as halofuginone or other quinazolinone derivatives and tranilast, (bb) endothelialization facilitators such as VEGF and RGD peptide, and (cc) blood rheology modulators such as pentoxifylline.

[0057] Numerous additional therapeutic agents useful for the practice of the present invention are also disclosed in U.S. Patent No. 5,733,925 assigned to NeoRx Corporation, the entire disclosure of which is incorporated by reference.

[0058] A wide range of therapeutic agent loadings can be used in connection with the medical devices of the present invention, with the amount of loading being readily determined by those of ordinary skill in the art and ultimately depending, for example, upon the condition to be treated, the nature of the therapeutic agent itself, the means by which the therapeutic agent is administered to the intended subject, and so forth.

[0059] In general, the release layers of the present invention are formed using any

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appropriate technique known in the art. Solvent-based techniques are preferred, in which the above-described first and second polymers are dissolved or dispersed in a solvent system prior to layer formation.

[0060] Where solvent-based techniques are used, the solvent system that is selected will contain one or more solvent species. The solvent system preferably is a good solvent for the polymers and, where included, for the therapeutic agent as well. The particular solvent species that make up the solvent system may also be selected based on other characteristics including drying rate and surface tension.

[0061] Solvent species that can be used in connection with the present invention include any combination of one or more of the following: (a) water, (b) alkanes such as ethane, hexane, octane, cyclohexane, heptane, isohexane, butane, pentane, isopentane, 2,2,4-trimethylpentane, nonane, decane, dodecane, hexadecane, eicosane, methylcyclohexane, cis-decahydronaphthalene and trans-decahydronaphthalene, (c) aromatic species such as benzene, toluene, xylene(s), naphthalene, styrene, ethylbenzene, 1-methylnaphthalene, 1,3,5-trimethylbenzene, tetrahydronaphthalene, diphenyl and 1,4-diethylbenzene, (d) halohydrocarbons including (i) chlorohydrocarbons such as chloroform, methyl chloride, dichloromethane, 1,1-dichloroethylene, ethylene dichloride, ethylidene chloride, propyl chloride, cyclohexyl chloride, 1,1,1-trichloroethane, perchloroethylene, trichloroethylene, butyl chloride, carbon tetrachloride, tetrachloroethylene, chlorobenzene, o-dichlorobenzene, benzyl chloride, trichlorobiphenyl, methylcyclohexane, 1,1,2,2-tetrachloroethane (ii) fluorinated halogenated species such as chlorodifluoromethane, dichlorofluoromethane, dichlorodifluoromethane, trichlorofluoromethane, 1,2-dichlorotetrafluoroethane, 1,1,2-trichlorotrifluoroethane, perfluor(methylcyclohexane), perfluor(dimethylcyclohexane) and (iii) other halohydrocarbons such as ethyl bromide, ethylidene bromide, ethylene dibromide, tribromomethane, bromotrifluoromethane, 1,1,2,2-tetrabromoethane, bromobenzene, bromochloromethane, 1-bromonaphthalene, methyl iodide, methylene diiodide (e) acid aldehydes/anhydrides such as acetaldehyde, furfural, butyraldehyde, benzaldehyde, acetyl chloride, succinic anhydride and acetic anhydride, (f) alcohols including (i) phenols such as phenol, 1,3-benzenediol, m-cresol, o-methoxyphenol, methyl salicylate and nonylphenol, (ii) polyhydric alcohols such as ethylene glycol, glycerol, propylene glycol, 1,3-butanediol, diethylene glycol, triethylene glycol, hexylene

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glycol and dipropylene glycol, and (iii) other alcohols such as methanol, ethanol, ethylene cyanohydrin, allyl alcohol, 1-propanol, 2-propanol, 3-chloropropanol, furfuryl alcohol, 1-butanol, 2-butanol, benzyl alcohol, isobutanol, cyclohexanol, 1-pentanol, 2-ethyl-1-butanol, diacetone alcohol, 1,3-dimethyl-1-butanol, ethyl lactate, butyl lactate, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, ethylene glycol monobutyl ether, 2-ethyl-1-hexanol, 1-octanol, 2-octanol, diethylene glycol monobutyl ether, 1-decanol, 1-tridecyl alcohol, nonyl-phenoxy ethanol, oleyl alcohol, triethylene glycol mono-oleyl ether, (g) ethers such as, epichlorohydrin, furan, 1,4-dioxane, dimethoxymethane, diethyl ether, bis-(2-chloroethyl) ether, anisole, di-(2-methoxyethyl) ether, dibenzyl ether, di-(2-chloroisopropyl) ether, bis-(m-phenoxyphenol) ether, dimethyl ether and tetrahydrofuran, (h) ketones, such as acetone, cyclohexanone, isophorone, diethyl ketone, mesityl oxide, acetophenone, methyl ethyl ketone, methyl isoamyl ketone, methyl isobutyl ketone, and methyl propyl ketone, (i) acids such as formic acid, acetic acid, benzoic acid, butyric acid, octanoic acid, oleic acid, stearic acid, (j) esters/acetates such as ethylene carbonate, butyrolactone, propylene-1,2-carbonate, ethyl chloroformate, ethyl acetate, trimethyl phosphate, diethyl carbonate, diethyl sulfate, ethyl formate, methyl acetate, n-butyl acetate, isobutyl acetate, t-butyl acetate, 2-ethoxyethyl acetate, isoamyl acetate, dimethyl phthalate, ethyl cinnamate, triethyl phosphate, diethyl phosphate, butyl benzyl phthalate, dibutyl phthalate, diethyl phthalate, tricrysyl phosphate, tributyl phosphate, dibutyl sebacate, methyl oleate, dioctyl phthalate, dibutyl stearate isopropyl acetate, isobutyl isobutyrate, n-propyl acetate and n-butyl propionate, (k) nitrogen compounds such as acetonitrile, acrylonitrile, propionitrile, butyronitrile, nitromethane, nitroethane, 2-nitropropane, nitrobenzene, ethanolamine, ethylenediamine, 1,1-dimethylhydrazine, 2-pyrrolidone, pyridine, propylamine, morpholine, analine, n-methyl-2-pyrrolidone, butylamine, diethylamine, cyclohexylamine, quinoline, dipropylamine, formamide, n,n-dimethylformamide, n,n-dimethylacetamide, tetramethylurea, hexamethyl phosphoramide, diethylenetriamine, triethylamine and triethanolamine, and (l) sulfur compounds such as carbon disulfide, dimethylsulfoxide, ethanethiol, dimethyl sulfone and diethyl sulfide.

[0062] Preferred solvent-based techniques include, but are not limited to, solvent

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casting techniques, spin coating techniques, web coating techniques, solvent spraying techniques, dipping techniques, techniques involving coating via mechanical suspension, including air suspension, ink jet techniques, electrostatic techniques, and combinations of these processes. Typically, a solution containing solvent and polymers (and, in some cases, a therapeutic agent) is applied to a substrate to form a release layer (e.g., a carrier layer or barrier layer). The substrate is typically all or a portion of an implantable or insertable medical device, to which the release layer is applied.

[0063] Where appropriate, techniques such as those listed above can be repeated or combined to build up a release layer to a desired thickness. The thickness of the release layer can be varied in other ways as well. For example, in one preferred process, solvent spraying, coating thickness can be increased by modification of coating process parameters, including increasing spray flow rate, slowing the movement between the substrate to be coated and the spray nozzle, providing repeated passes and so forth.

[0064] In the case where a carrier layer is being established, a therapeutic agent can be included in the above-described polymer solution if desired, and hence co-established with the carrier layer. In other embodiments, on the other hand, the therapeutic agent can be dissolved or dispersed within a solvent, and the resulting solution contacted with a previously formed carrier layer, for example, using one or more of the application techniques described above (e.g., dipping, spraying, etc.).

[0065] Barrier layers, on the other hand, are formed over a therapeutic-agent-containing region. In some embodiments, however, the therapeutic-agent-containing region comprises one or more polymers, which can be selected, for example, from the polymers listed above. As such, the therapeutic-agent-containing region can also be established using solvent-based techniques (e.g., dipping, spraying, etc.) such as those discussed above. In other embodiments, the therapeutic-agent-containing region beneath the barrier layer is established without an associated polymer. For example, the therapeutic agent can simply be dissolved or dispersed in a liquid, and the resulting solution/dispersion contacted with a substrate, for instance, using one or more of the above-described application techniques.

[0066] Where the release layer is formed using a solvent based technique, it is preferably dried after application to remove the solvents. The release layer typically further conforms to the underlying surface during the drying process.

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[0067] The invention is further described with reference to the following non-limiting Examples.

#### EXAMPLE 1

[0068] Solutions are provided that contain 99 wt% chloroform, 0.25 wt% paclitaxel and 0.75 wt% of a polymer composition or blend.

[0069] One solution is prepared by mixing 0.75 wt% of the block copolymer polystyrene-polyisobutylene-polystyrene block copolymer (SIBS) with the solvent and paclitaxel.

The SIBS copolymer is synthesized using known techniques such as those described in U.S. Patent No. 5,741,331, U.S. Patent No. 4,946,899 and U.S. Serial No. 09/734,639.

[0070] A second solution is prepared by mixing 0.75 wt% of the block copolymer polystyrene-polyvinylpyrrolidone (PS/PVP) with the solvent and paclitaxel. The PS/PVP copolymer is available from International Specialty Products Corporation (ISP) as Agrimer™ ST.

[0071] A third solution is prepared by blending 0.30% of the PS/PVP copolymer and 0.45% of the SIBS copolymer with the solvent and paclitaxel.

[0072] All solutions are prepared by (1) mixing the paclitaxel and a small amount of the chloroform, (2) adding the polymer or copolymers, (3) adding the remaining chloroform, (4) thoroughly mixing (e.g., overnight), and (5) filtering.

[0073] The solution is then placed in a syringe pump and fed to a spray nozzle. A stent is mounted onto a holding device parallel to the nozzle and, if desired, rotated to ensure uniform coverage. Depending on the spray equipment used, either the component or spray nozzle can be moved while spraying such that the nozzle moves along the component while spraying for one or more passes. After a carrier coating is formed in this fashion, the stent is dried, for example, by placing it in a preheated oven for 30 minutes at 65°C, followed by 3 hours at 70°C.

[0074] Three stents are formed in this manner for each of the various solutions.

[0075] Paclitaxel release is then measured as a function of time in PBS containing 0.5 wt% Tween® 20 (polyoxyethylene(20) sorbitan monolaurate) available from Sigma-Aldrich. The results, presented as the cumulative release of paclitaxel as a function of time, are graphically illustrated in Fig. 1.

[0076] These results indicate that the release rate of a therapeutic agent from a

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polymeric carrier layer can be modulated by changing the ratio of the hydrophilic and hydrophobic polymeric components by blending a hydrophobic polymeric drug carrier with a block copolymer containing at least one hydrophilic polymer chain and at least one hydrophilic polymer chain.

#### EXAMPLE 2

[0077] A series of solutions are prepared in a procedure similar to the procedure used in Example 1. All solutions contain the following: 25 wt% tetrahydrofuran (THF), 74 wt% toluene, 0.25 wt% paclitaxel and 0.75 wt% of a polymer composition or blend.

[0078] Solutions are made containing the following polymeric constituents: (a) 0.05 wt% of a polystyrene-polyacrylic acid-polystyrene triblock copolymer (PS-PAA-PS) with block lengths of 3.3k-13.5k-3.3k, respectively, and 0.70 wt% SIBS, and (b) 0.05 wt% of a polystyrene-polyacrylic acid diblock copolymer (PS-PAA) with block lengths of 4.3k-19.5k, respectively, and 0.70 wt% SIBS. The PS-PAA-PS and PS-PAA copolymers are available from the Polymer Source, Inc.

[0079] All solutions are prepared by (1) mixing the paclitaxel and THF, (2) adding the polymer or copolymers, (3) adding the toluene, (4) thoroughly mixing (e.g., overnight), and (5) filtering.

[0080] The solutions are applied to stents and dried according to the procedures of Example 1. Three stents are coated using each of the above solutions. The cumulative release of paclitaxel as a function of time is then measured as in Example 1. The results are graphically illustrated in Fig. 2.

[0081] These results indicate that the release rate of a therapeutic agent from a polymeric carrier layer can be modulated by changing the ratio of the hydrophilic and hydrophobic polymeric components by blending a hydrophobic polymeric drug carrier with a block copolymer that contains at least one hydrophilic polymer chain and at least one hydrophobic polymer chain.

#### EXAMPLE 3

[0082] A series of solutions are prepared in a procedure similar to the procedure used in Example 1. The solutions contain the following: dimethyl acetamide (DMAc), toluene, 0.25 wt% paclitaxel and 0.75 wt% of a polymer composition or blend.

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[0083] The solutions are made containing the following polymeric constituents: (a) 0.05 wt% of a polystyrene-polyacrylamide diblock copolymer (PS-Polyacrylamide) with block lengths of 16.5k-4.4k, respectively, and 0.70 wt% SIBS, (b) 0.05 wt% of a polystyrene-polyacrylate sodium salt diblock copolymer (PS-Polyacrylate (Na salt)) with block lengths of 3.5k-34.5k, respectively, and 0.70 wt% SIBS. The PS-Polyacrylamide and PS-Polyacrylate (Na salt) copolymers are available from the Polymer Source, Inc.

[0084] All solutions are prepared by (1) mixing the paclitaxel and 15-17 wt% DMAc, (2) adding the polymers or copolymers, (3) adding 84-82 wt% toluene as required to make a solution with 1.0 wt% total solids, (4) thoroughly mixing (e.g., overnight), and (5) filtering

[0085] The solutions are applied to stents and dried according to the procedures of Example 1. Three stents are coated using each of the above solutions. The cumulative release of paclitaxel as a function of time is then measured as in Example 1. The results are graphically illustrated in Fig. 3.

[0086] These results indicate that the release rate of a therapeutic agent from a polymeric carrier layer can be modulated by changing the ratio of the hydrophilic and hydrophobic polymeric components by blending a hydrophobic polymeric drug carrier with a block copolymer that contains at least one hydrophilic polymer chain and at least one hydrophobic polymer chain.

#### EXAMPLE 4

[0087] A series of solutions are prepared in a procedure similar to the procedure used in Example 1. All solutions contain the following: 99% chloroform, 0.25 wt% paclitaxel and 0.75 wt% of a polymer composition or blend.

[0088] The control solution is prepared by mixing 0.75 wt% the SIBS copolymer (see Example 1) with the solvent and paclitaxel.

[0089] Test solutions are made containing the following polymeric constituents: (a) 0.15 wt% Polystyrene-co-polyethylene oxide-co-polystyrene triblock copolymer (PS-PEO-PS) with block lengths of 9.5k-49k-9.5k, respectively, and 0.60 wt% SIBS, (b) 0.15 wt% Polyethylene oxide-co-polystyrene-co-polystyrene triblock copolymer (PEO-PS-PEO) with block lengths of 6.3k-1.7k-6.3k, respectively, and 0.60 wt% SIBS, (c) 0.10 wt% Polystyrene-co-polyethylene oxide diblock copolymer (PS-PEO) with block lengths

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of 58.6k-71k, and 11k-41.9k, respectively, and 0.65 wt% SIBS. The polystyrene and polyethylene oxide diblock and triblock copolymers are available from the Polymer Source, Inc.

[0090] The solutions are applied to stents and dried according to the procedures of Example 1. Three stents are coated using each of the above solutions. The cumulative release of paclitaxel as a function of time is then measured as in Example 1. The results are graphically illustrated in Fig. 4.

[0091] These results indicate that the release rate of a therapeutic agent from a carrier layer comprising a hydrophobic polymeric carrier can be modulated by the addition of block copolymers with hydrophilic and hydrophobic polymer chains. The results also show that the release rate is a function of the polymer structure (i.e. triblock copolymer compared to a diblock copolymer), and may be altered by changing the relative amount of the hydrophilic and hydrophobic polymer chains of the block copolymer.

[0092] Although various embodiments are specifically illustrated and described herein, it will be appreciated that modifications and variations of the present invention are covered by the above teachings and are within the purview of the appended claims without departing from the spirit and intended scope of the invention.



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IN THE CLAIMS:

1. A therapeutic-agent-releasing medical device comprising:
  - (a) an implantable or insertable medical device;
  - (b) a release layer disposed over at least a portion of the implantable or insertable medical device, said release layer comprising (i) a first polymer comprising one or more polymer chains that form one or more polymer phase domains when the first polymer is in a pure solid-state form; and (ii) a second polymer comprising two or more polymer chains that form two or more phase domains when the second polymer is in a pure solid-state form, wherein at least one polymer chain in the second polymer is compatible with at least one polymer chain in the first polymer; and
  - (c) a therapeutic agent, wherein said release layer regulates the rate of release of the therapeutic agent from the medical device upon implantation or insertion of the device into a patient.
2. The medical device of claim 1, wherein said first polymer forms a single phase domain and is selected from a homopolymer, a random copolymer and an alternating copolymer.
3. The medical device of claim 1, wherein said first polymer forms two or more phase domains and is selected from a block copolymer and a graft copolymer.
4. The medical device of claim 1, wherein said second polymer is a graft copolymer.
5. The medical device of claim 1, wherein said second polymer is a block copolymer.
6. The medical device of claim 1, wherein one of said polymer chains in said first polymer is formed from the same monomer or monomers as is one of said polymer chains of said second polymer.
7. The medical device of claim 1, wherein said release layer is a barrier layer disposed over a therapeutic-agent-containing region that comprises said therapeutic agent.

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8. The medical device of claim 1, wherein said release layer is a carrier layer comprising said therapeutic agent.
9. The medical device of claim 1, wherein said first polymer is a block or graft copolymer comprising (i) one or more polyolefin polymer chains and (ii) one or more vinyl aromatic polymer chains.
10. The medical device of claim 9, wherein said first polymer is a block or graft copolymer comprising (i) one or more polyisobutylene polymer chains and (ii) one or more styrenic polymer chains.
11. The medical device of claim 10, wherein said second polymer is a block or graft copolymer comprising (i) one or more polyisobutylene polymer chains and (ii) one or more chains selected from polyethylene oxide; polyvinylpyrrolidone; polyacrylamide; polydimethylacrylamide; polyacrylic acid and salts thereof; polymethacrylic acid and salts thereof; poly(maleic anhydride) and partial esters, free acids and acid salts thereof; polyvinyl alcohol and fully and partially hydrolyzed derivatives thereof; and poly(vinyl pyridine).
12. The medical device of claim 10, wherein said second polymer is a block or graft copolymer comprising (i) one or more styrenic polymer chains and (ii) one or more chains selected from polyethylene oxide; polyvinylpyrrolidone; polyacrylamide; polydimethylacrylamide; polyacrylic acid and salts thereof; polymethacrylic acid and salts thereof; poly(maleic anhydride) and partial esters, free acids and acid salts thereof; polyvinyl alcohol and fully and partially hydrolyzed derivatives thereof; and poly(vinyl pyridine).
13. The therapeutic-agent-releasing medical device of claim 1, wherein said implantable or insertable medical device is selected from a catheter, a guide wire, a balloon, a filter, a stent, a stent graft, a vascular graft, a vascular patch, a shunt, and an intraluminal paving system.

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14. The therapeutic-agent-releasing medical device of claim 1, wherein said implantable or insertable medical device is adapted for implantation or insertion into the coronary vasculature, peripheral vascular system, esophagus, trachea, colon, biliary tract, urinary tract, prostate or brain.
15. The therapeutic-agent-releasing medical device of claim 1, wherein said therapeutic agent is selected from one or more of the group consisting of an anti-thrombotic agent, an anti-proliferative agent, an anti-inflammatory agent, an anti-migratory agent, an agent affecting extracellular matrix production and organization, an antineoplastic agent, an anti-mitotic agent, an anesthetic agent, an anti-coagulant, a vascular cell growth promoter, a vascular cell growth inhibitor, a cholesterol-lowering agent, a vasodilating agent, and an agent that interferes with endogenous vasoactive mechanisms.
16. A method of modulating the release rate of a therapeutic agent from a medical device comprising:
  - providing a medical device comprising: (a) an implantable or insertable medical device; (b) a release layer disposed over at least a portion of the implantable or insertable medical device, said release layer comprising a first polymer which comprises one or more polymer chains that form one or more polymer phase domains when said first polymer is in a pure solid-state form, and (c) a therapeutic agent, said release layer regulating the rate of release of the therapeutic agent from the medical device upon implantation or insertion of the device into a patient; and
  - modulating the release rate from said medical device by adding to said release layer a second polymer which comprises two or more polymer chains that form two or more phase domains when said second polymer is in a pure solid-state form, wherein at least one polymer chain in said second polymer is compatible with at least one polymer chain in said first polymer.
17. The method of claim 16, wherein said first polymer comprises at least one hydrophobic polymer chain, and wherein said second polymer comprises (a) at least

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one hydrophilic polymer chain and (b) at least one hydrophobic polymer chain that is compatible with said hydrophobic polymer chain of said first polymer.

18. The method of claim 17, wherein (a) said first polymer comprises a hydrophobic styrenic polymer chain and (b) said second polymer comprises (i) a hydrophobic styrenic polymer chain and (ii) one or more hydrophilic chains selected from polyethylene oxide; polyvinylpyrrolidone; polyacrylamide; polydimethylacrylamide; polyacrylic acid and salts thereof; polymethacrylic acid and salts thereof; poly(maleic anhydride) and partial esters, free acids and acid salts thereof; polyvinyl alcohol and fully and partially hydrolyzed derivatives thereof; and poly(vinyl pyridine).
19. The method of claim 17, wherein said first polymer is a block or graft copolymer comprising (i) one or more hydrophobic olefin polymer chains and (ii) one or more hydrophobic vinyl aromatic polymer chains.
20. The method of claim 19, wherein said first polymer is a block or graft copolymer comprising (i) one or more hydrophobic polyisobutylene chains and (ii) one or more hydrophobic styrenic polymer chains.
21. The method of claim 20, wherein said second polymer is a block or graft copolymer comprising (i) one or more hydrophobic polyisobutylene chains and (ii) one or more chains selected from polyethylene oxide; polyvinylpyrrolidone; polyacrylamide; polydimethylacrylamide; polyacrylic acid and salts thereof; polymethacrylic acid and salts thereof; poly(maleic anhydride) and partial esters, free acids and acid salts thereof; polyvinyl alcohol and fully and partially hydrolyzed derivatives thereof; and poly(vinyl pyridine).
22. The method of claim 20, wherein said second polymer is a block or graft copolymer comprising (i) one or more hydrophobic styrenic polymer chains and (ii) one or more chains selected from polyethylene oxide; polyvinylpyrrolidone; polyacrylamide; polydimethylacrylamide; polyacrylic acid and salts thereof; polymethacrylic acid and salts thereof; poly(maleic anhydride) and partial esters, free acids and acid salts

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thereof; polyvinyl alcohol and fully and partially hydrolyzed derivatives thereof; and poly(vinyl pyridine).

23. The method of claim 16, wherein said second polymer composition renders said release layer more hydrophilic.
24. The method of claim 16, wherein said second polymer composition renders said release layer less hydrophilic.
25. A method of forming the therapeutic-agent-releasing medical device of claim 1, comprising: (a) providing a solution comprising: one or more solvents, said first polymer and said second polymer; (b) applying said solution to a surface of said implantable or insertable medical device; and (c) removing said solvents from said solution to form said release layer.
26. The method of claim 25, wherein said solution further comprises said therapeutic agent.
27. The method of claim 25, wherein said solution is applied over a therapeutic-agent-containing region that comprises said therapeutic agent.
28. The method of claim 25, wherein said solution is applied by a solvent spraying technique.
29. A method of administering a therapeutic agent to a patient comprising (a) providing the therapeutic-agent-releasing medical device of claim 1 and (b) implanting or inserting the therapeutic-agent-releasing medical device of into said patient.
30. The method of claim 29, wherein said medical device is selected from a catheter, a guide wire, a balloon, a filter, a stent, a stent graft, a vascular graft, a vascular patch, a shunt, and an intraluminal paving system.

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31. The method of claim 29, wherein said medical device is inserted into the vasculature.
32. The method of claim 29, wherein said therapeutic agent is released in the treatment of restenosis.

Stent ctg.: 75% Polymer / 25% Paclitaxel  
Polym: PS / PVP copolymer / SIBS  
PVP: Polyvinylpyrrolidone

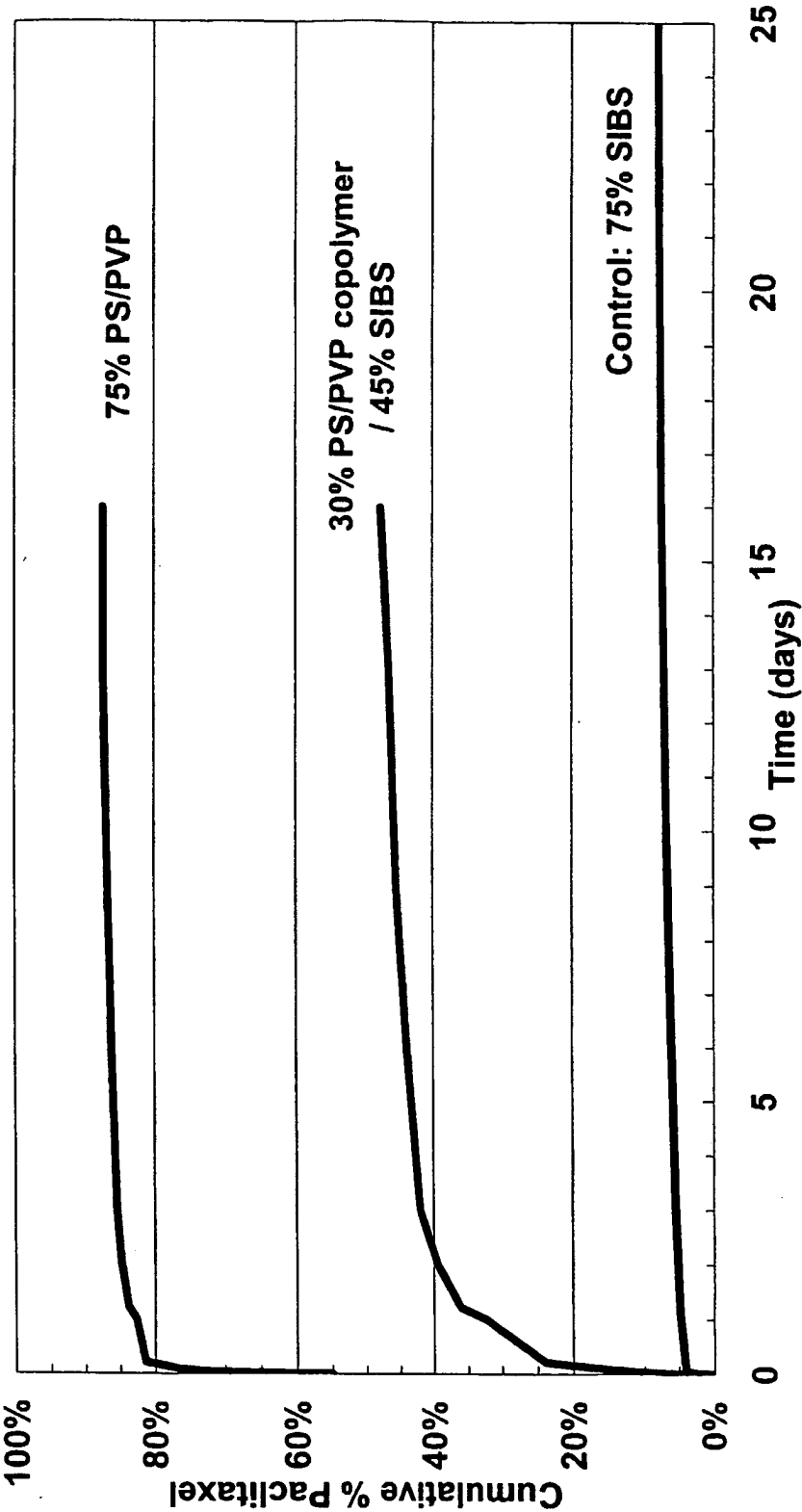


Fig. 1

Stent ctg.: 75% Polymer / 25% Paclitaxel  
Polym: 5% PS-PAA diblock or triblock copolymer / 70% SIBS  
PAA: Polyacrylic acid

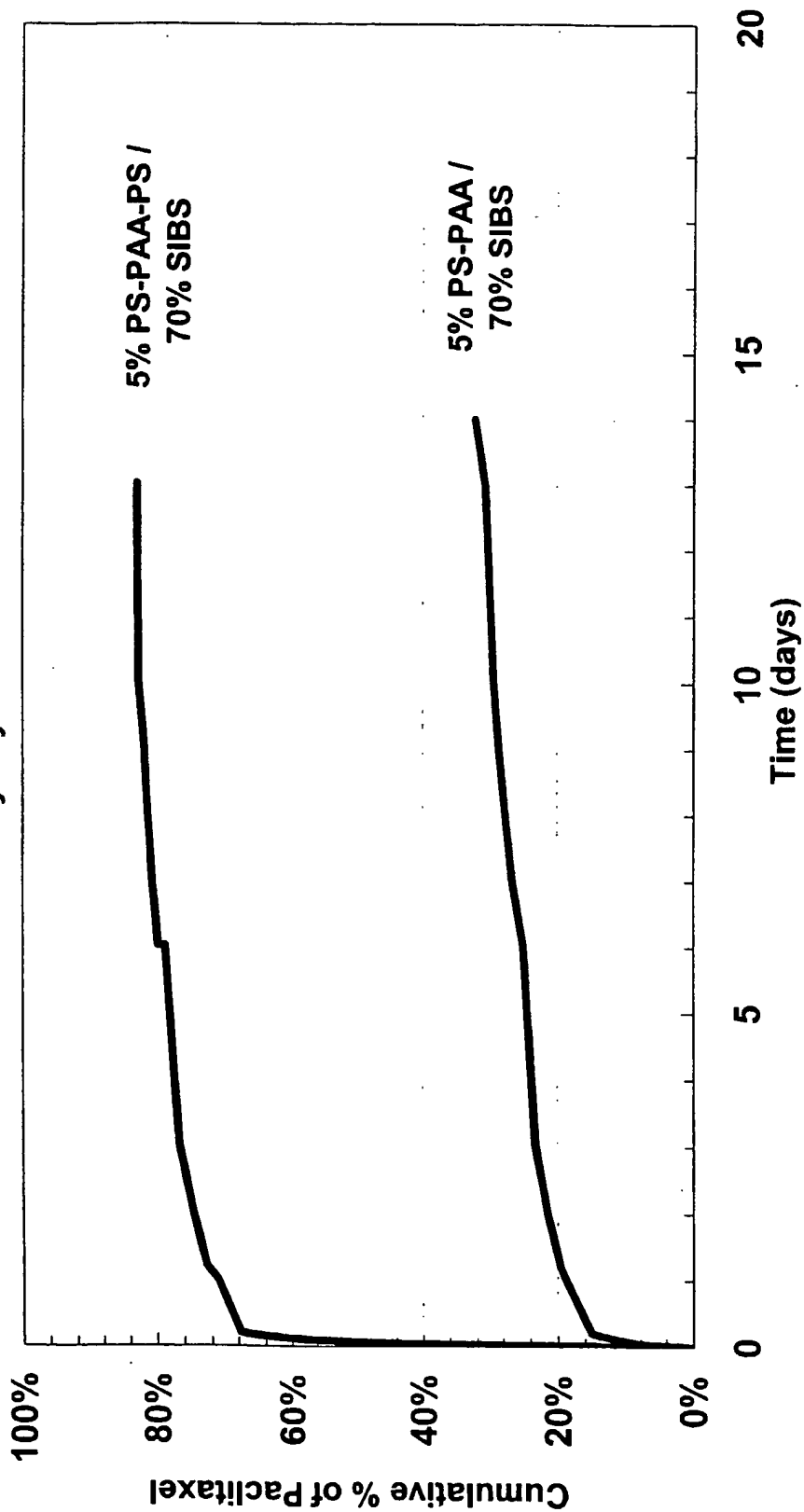


Fig. 2



Stent ctg.: 75% Polymer / 25% Paclitaxel  
Polym: PS based di & triblock copolymer / SIBS

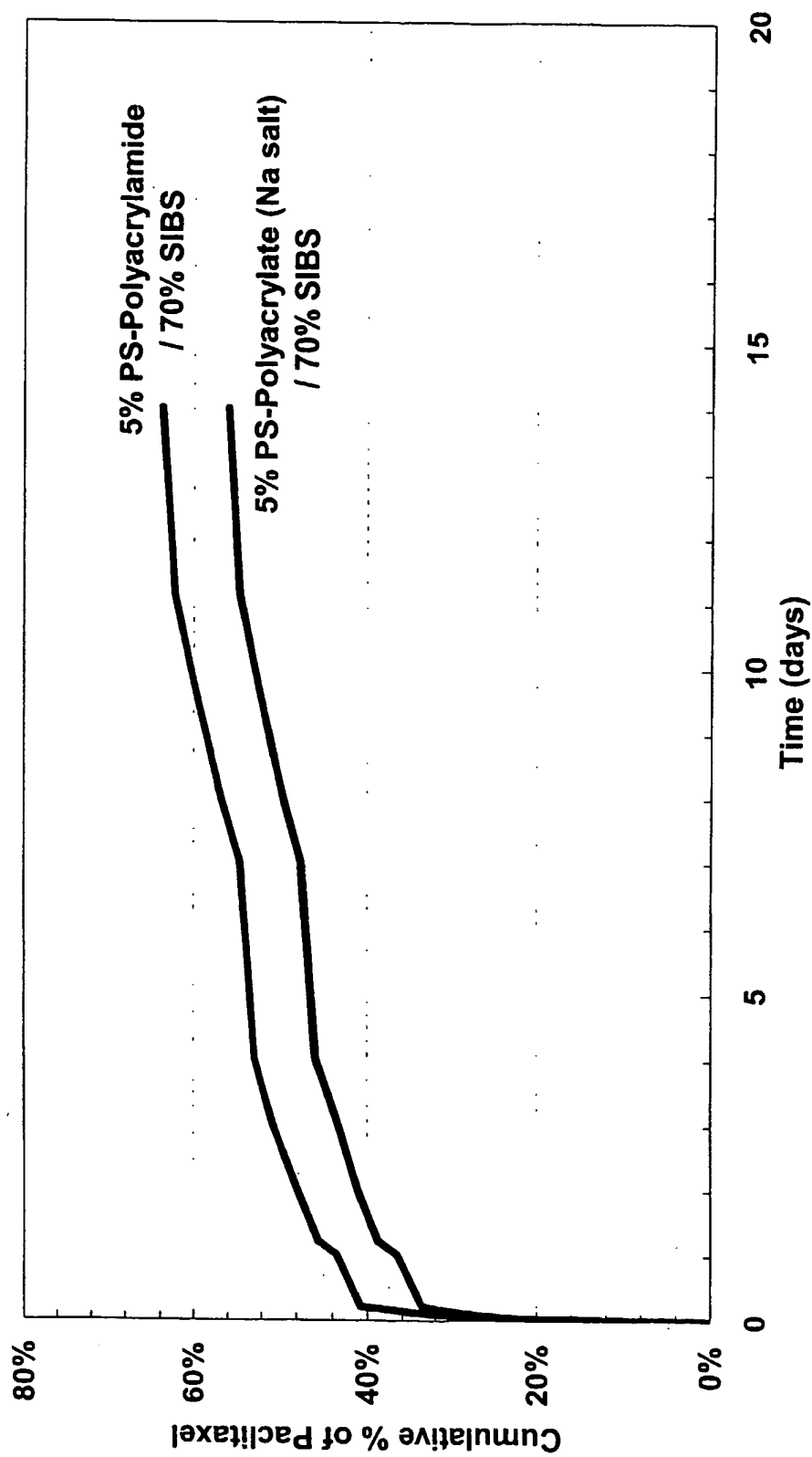


Fig. 3

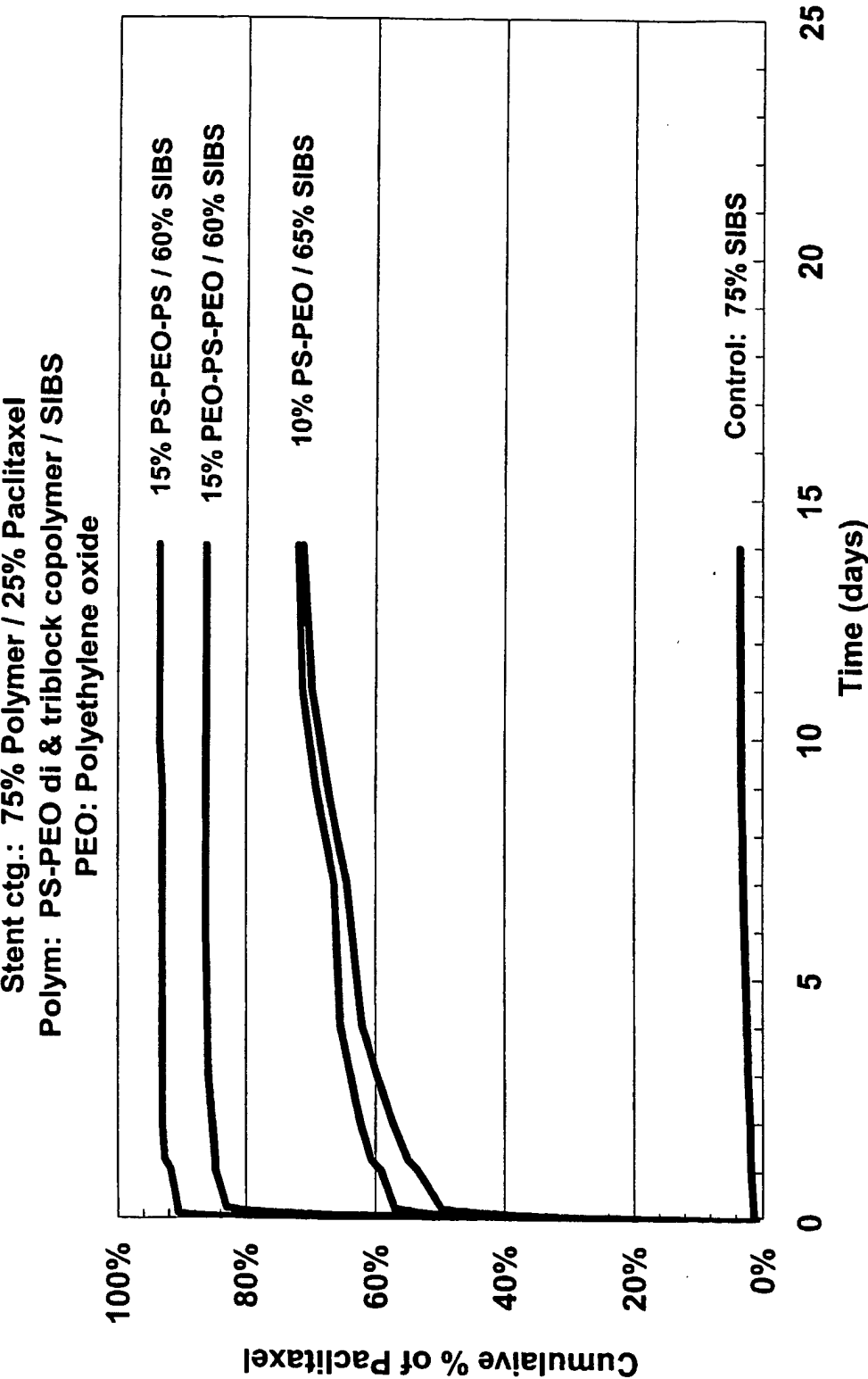


Fig. 4

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61L27/34 A61L27/56 A61L31/16 A61L31/10 A61L29/08  
A61L29/16

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 41647 A (LEVY ROBERT J ; PHILADELPHIA CHILDREN HOSPITAL (US)) 20 July 2000 (2000-07-20) page 6, line 15 - page 7, line 15; claims page 27, line 11 - line 25 ---	1-32
X	WO 86 02006 A (BAXTER TRAVENOL LAB) 10 April 1986 (1986-04-10) page 4, line 8 - line 17; claims ---	1-32
X	WO 84 01721 A (BAXTER TRAVENOL LAB) 10 May 1984 (1984-05-10) page 4, line 10 - line 19; examples ---	1-32
X	EP 0 328 421 A (UNIV COLUMBIA) 16 August 1989 (1989-08-16) page 5, line 1 - line 50; claims page 7, line 1 - line 29 ---	1-32
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

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Date of the actual completion of the international search

20 November 2003

Date of mailing of the international search report

04/12/2003

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Authorized officer

ESPINOSA, M

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 62830 A (SCIMED LIFE SYSTEMS INC) 26 October 2000 (2000-10-26) page 10, line 22 - line 26; claims ---	1-32
P,X	WO 02 47731 A (SCIMED LIFE SYSTEMS INC) 20 June 2002 (2002-06-20) cited in the application page 28, line 1 -page 29, line 6; claims ---	1-32
P,X	WO 03 035135 A (SCIMED LIFE SYSTEMS INC) 1 May 2003 (2003-05-01) page 4, line 1 - line 30; claims -----	1-32

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/19309

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 29-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/19309

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0041647	A	20-07-2000	US 6395029 B1 AU 2853700 A WO 0041647 A1	28-05-2002 01-08-2000 20-07-2000
WO 8602006	A	10-04-1986	US 4603152 A AU 582796 B2 AU 4861885 A EP 0197068 A1 JP 62500432 T WO 8602006 A1 US 4677143 A ZA 8507530 A	29-07-1986 13-04-1989 17-04-1986 15-10-1986 26-02-1987 10-04-1986 30-06-1987 28-05-1986
WO 8401721	A	10-05-1984	AU 2039883 A CA 1224717 A1 EP 0124536 A1 ES 8504464 A1 WO 8401721 A1 US 4603152 A	22-05-1984 28-07-1987 14-11-1984 16-07-1985 10-05-1984 29-07-1986
EP 0328421	A	16-08-1989	US 5019096 A AT 88096 T AU 2989589 A AU 636767 B2 AU 7922991 A CA 1341224 C DE 68905939 D1 DE 68905939 T2 EP 0328421 A2 JP 2017071 A JP 7090039 B US 5133090 A US 5616338 A	28-05-1991 15-04-1993 17-08-1989 06-05-1993 03-10-1991 01-05-2001 19-05-1993 05-08-1993 16-08-1989 22-01-1990 04-10-1995 28-07-1992 01-04-1997
WO 0062830	A	26-10-2000	US 6368658 B1 AU 4465300 A CA 2368962 A1 EP 1171245 A2 JP 2003524465 T WO 0062830 A2 US 2002127327 A1 US 2001022988 A1	09-04-2002 02-11-2000 26-10-2000 16-01-2002 19-08-2003 26-10-2000 12-09-2002 20-09-2001
WO 0247731	A	20-06-2002	US 2002107330 A1 AU 3085102 A EP 1341565 A2 WO 0247731 A2	08-08-2002 24-06-2002 10-09-2003 20-06-2002
WO 03035135	A	01-05-2003	WO 03035135 A1 US 2003059454 A1	01-05-2003 27-03-2003

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